CPH-ASSIST

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Propensity matched analysis of intravenous thrombolysis versus bridging thrombolysis followed by endovascular thrombectomy

Danish Summary

Baggrund

Der har længe hersket en opfattelse af, at randomiserede kontrollerede forsøg inden for den endovaskulære behandling af akut apopleksi, har været vanskelige at udføre. Samtidig er stadig flere endovaskulære teknikker i form af kombineret intraarteriel – og intravenøs (IV) trombolyse ('bridging' trombolyse) og trombektomi blevet indført i klinikken, på trods af manglende evidens for deres gavnlige effekt. Dels har mange apopleksibehandlende læger været tilbageholdende med at udføre randomiserede kliniske forsøg med de endovaskulære metoder, som følge af lægernes empiribasserede overbevisning om metodernes overlegenhed over IV trombolyse, og dels har de hidtidige observationelle studier og metaanalyser ikke kunnet retfærdiggøre udførelsen af randomiserede forsøg.

Således må effekten af endovaskulær behandling undersøges i ikke-randomiserede longitudinelle forsøg. Imidlertid er bias næsten uundgåelige i disse forsøgsdesign. For at reducere bias og øge styrken i de longitudinelle studier er der udviklet avancerede statistiske metoder i form af propensity- og multivariatanalyse. Disse metoder justerer de patientrelaterede faktores betydning for udfaldet af behandlingen og estimerer sandsynligheden for, at en patient modtager en given behandling, som følge disse faktorer. Under forudsætning af et a priori kendskab til forhold, der kan påvirke et givent behandlingsudfald, kan metoderne reducere bias i ikke-randomiserede undersøgelser. Vi mener, at vi ved anvendelse af propensity- og multivariatanalyse af data fra omfattende observationalle databaser, som led i **C**o**p**en**h**agen **a**cute **s**evere **s**troke **i**ntervention **st**udy (CPH-ASSIST), vil kunne påvise en større gavnlig effekt af behandlingen af patienter med akut apopleksi med trombektomi og 'bridging' trombolyse end med behandling med IV trombolyse alene. Endvidere vil vi udføre nedenstående supplerende studier med henblik på at belyse og forbedre flere aspekter af behandlingen af akut apopleksi.

I første supplerende studie vil vi undersøge bivirkningerne ved apopleksibehandling. Det er velkendt at apopleksibehandling med IV trombolyse, 'bridging' trombolyse og trombektomi kan være forbundet med alvorlige bivirkninger, såsom symptomatiske og fatale intrakranielle blødninger. Imidlertid er det som følge af manglen på randomiserede undersøgelser endnu uvist, om den gavnlige effekt af behandlingen overstiger de alvorlige bivirkninger. Som led i CPH-ASSIST studiet vil vi undersøge dette aspekt, med henblik på at frembringe viden, der fremadrettet vil kunne bidrage til beslutningen om hvilken form for behandling, der skal iværksættes hos den enkelte patient, som rammes af akut apopleksi.

I det andet supplerende studie vil vi undersøge, om tilstedeværelsen af kollateral cerebral blodforsyning forbedrer prognosen for apopleksiramte patienter. Det er en generel erfaring blandt apopleksibehandlende læger, at tilstedeværelsen og omfanget af kollateral cerebral blodforsyning i høj grad determinerer behandlingsresponset og prognosen. Dette forhold er imidlertid endnu ikke kvantitativt undersøgt. Vi vil kvantitere den cerebrale kollaterale blodforsyning hos apopleksipatienter i CPH-ASSIST kohorten ved brug af stereologisk metode appliceret på CT angiogrammer (CTA). Således håber vi at opnå, at den enkelte patients sandsynlige respons på behandlingen kan estimeres allerede ved udførelsen af CTA, således at patienten kan tilbydes den behandling, der har størst potentiel gavnlig effekt og lavest risiko for bivirkninger.

Endelig vil vi i det tredje supplerende studie, som led i CPH-ASSIST studiet, kortlægge forsinkelser i behandlingen af patienter ramt af akut apopleksi i hovedstadsområdet, idet undersøgelser har vist, at selv korte tidsintervaller med cerebral iskæmi markant forværrer prognosen for denne patientgruppe. Desuden vil vi estimere forværringen af patientens prognose over tid. Studiet vil således kunne identificere indsatsområder for logistisk effektivisering til gavn for patienterne og for samfundet som helhed.

Metode

Vi vil som led i CPH-ASSIST studiet udføre et retrospektivt kohorteforsøg, som forløber i perioden fra januar 2009 til januar 2013 og inkluderer patientdata fra tre københavnske hospitaler. Vi vil benytte avanceret statistisk metode til dataanalyse, herunder propensity matched analyse, og vi estimerer, at data fra 100 til 150 sammenlignelige par vil være tilstrækkeligt til at påvise en forskel i behandlingseffekten på 30%. Yderligere vil vi benytte de indsamlede data og de nævnte statistiske metoder til undersøgelse af bivirkninger, forsinkelser i behandlingen og betydningen af kollateral cerebral blodgennemstrømning i forbindelse med trombolyse- og trombektomibehandlingen af patienter med akut apopleksi.

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Propensity matched analysis of intravenous thrombolysis versus bridging thrombolysis followed by endovascular thrombectomy

Background

Randomized controlled trials in acute interventional stroke management have been notoriously difficult to perform. Even though no device or intervention has proven clinically effective to receive the label approved for treatment of acute ischemic stroke, growing numbers of devices receive labels for thrombus removal and gain access to acute stroke treatment through the back door. Availability of novel powerful diagnostic tests in the acute setting, such as non-invasive angiography and advanced tissue and perfusion imaging, empower the clinician to treat stroke based on physiological data. Substantial numbers of stroke specialists have become unwilling to enroll patients into ongoing acute interventional randomized trials because they consider endovascular therapy using clot removal devices superior to IV thrombolysis only. While soft surrogate markers, such as reperfusion, may deceive physicians from hard clinical endpoints, several observational studies and meta-analyses call into question the equipoise required for the performance of randomized controlled trials. Since non-randomized therapeutic trials are inherent to bias, advanced statistical methods aiming at reducing bias in observational trials have been introduced. Multivariate regression analysis targets to quantify the effect of patient characteristics on the recorded outcomes and propensity analysis targets to quantify the effect of patient characteristics on the treatment received. While these methods may successfully reduce bias, they require a priori knowledge of all characteristics impacting on outcome recorded or treatment received. Given the perceptions based on timely reperfusion and superiority of endovascular approaches outlined above, we feel that propensity matched analysis may be of particular interest in assessing large observational databases for differences in outcomes.

Description

Propensity matched analysis is perceived as a possible alternative for randomized clinical trials in some areas of highly specialized acute care (1). Some previous examples in stroke preventions trials teach us conformity (2, 3) of propensity matched analysis with the randomized controlled trial (RCT). While this approach has been used in acute management situations, such as decision-making in the treatment of infective endocarditis (1), it has not yet been applied to the acute stroke setting. The non-randomized nature of this approach may result in bias, however, at the time the patients were subjected to the different treatments, virtually no information was available that may have lead to systematic differences between those patients treated with IV thrombolysis only and those who received 'bridging' thrombolysis followed by endovascular thrombectomy. Advantages of retrospective propensity analysis include improving external trial validity, because all subsequent patients are considered for analysis as opposed to "cherry picking" patients into RCTs that often impair the utility of the trial results. This phenomenon is known to affect the coincidental enrollment of patients into a randomized trial (4).

Meta-analysis on clinical outcomes of 15 studies using the 'bridging' therapy approach showed a pooled estimate of 48.9% (95% CI, 42.9% - 54.9%) for favorable outcome, 17.9% (95% CI, 12.7% - 23.7%) for mortality and 8.6% (95% CI, 6.8% - 10.6%) for symptomatic intracranial hemorrhage. By using the control groups of IV Alteplase-treated patients in eight studies, 'bridging' therapy was associated with a favorable outcome (OR, 2.26; 95% CI, 1.16 - 4.40), but no differences in mortality or symptomatic intracranial hemorrhage outcomes were found (5).

A retrospective propensity analysis will be performed in patients who received IV-rtPA versus thrombectomy or 'bridging' therapy treatment at Copenhagen area hospitals (Glostrup, Bispebjerg and Roskilde Hospitals) in the years 2009 - 2010 and 2011 - 2012. This matched pair analysis will be adjusted with the propensity score and give an estimate how 'bridging' therapy and endovascular thrombectomy compares to standard IV thrombolysis only.

While the main focus of the entire thesis will be to create a comprehensive database and to compare IV thrombolysis versus 'bridging' therapy and endovascular thrombectomy in clinical practice, several important other secondary projects can be inferred from the same data set and are outlined as additional manuscripts.

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Main Hypothesis

• Thrombectomy or 'bridging' therapy provide better outcomes in patients with acute severe stroke and occlusion of major intracranial arteries than IV thrombolysis only.

Aims

1. To identify patients receiving IV thrombolysis and/or thrombectomy with NIHSS >9 and occlusion of major intracranial arteries in databases from three Copenhagen area hospitals.
2. To estimate propensity scores using criteria estimated with a probit model.
3. To perform superiority analysis between the two groups using composite and single end points.
4. To perform hazard ratio analysis for independent (mRS 0-2) and dependent outcome or death (mRS 3-6).

Methods

The study is a retrospective, observational cohort study conducted from January 2009 to January 2013 at three Copenhagen area hospitals as part of the **C**op**e**n**h**agen **a**cute **s**evere **s**troke **i**ntervention **st**udy (CPH-ASSIST). Data on the patients are extracted from a regional stroke database, the NIP registry and the hospital records. The stroke database is maintained since January 2009 at the Copenhagen University Hospitals, Bispebjerg and Rigshospitalet, and contains a retrospective and prospective part. We identified two groups of patients (Fig. 1). One group included patients with acute ischemic stroke who were treated with IV thrombolysis in the years 2009 – 2011 and the other group consisted of patients treated with thrombectomy in 2011 – 2012. Since 2004 the number of patients suffering from acute ischemic stroke treated with IV thrombolysis at Bispebjerg Hospital has rapidly increased.

As a general rule, patients eligible for IV thrombolysis must have a NIHSS of 5 (moderate stroke) or above, although in a minority of cases IV thrombolysis was initiated in patients with a lower NIHSS score due to special circumstances (Fig. 2).

Patients were identified by review of the hospitals' ED admission logs and matched by similar age, gender, risk factors, medication, co-morbidity and NIHSS. Only patients with a NIHSS > 9 were included in the study. Demographic characteristics, time from symptom onset to arrival at the thrombolysis center and interventional center, past medical history, and baseline neurologic examination results were obtained from the patients' pre-hospital records, medical records and the NIP database.

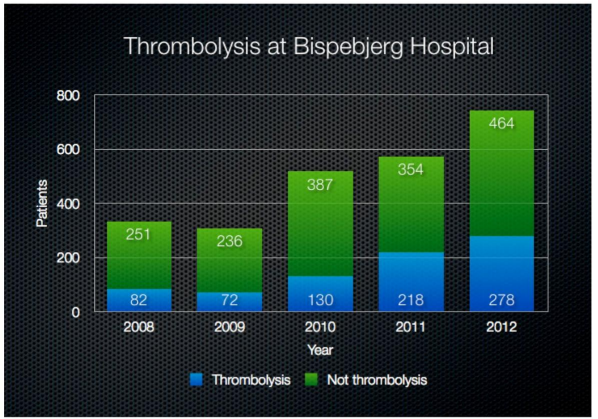

Figure 1. Number of patients receiving thrombolysis at Bispebjerg Hospital from 2008 to 2012.

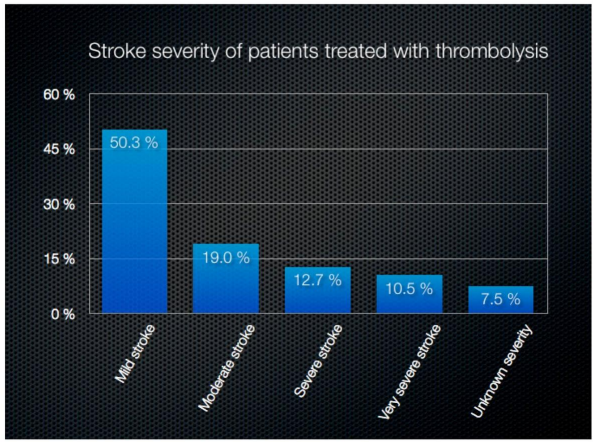

Figure 2. Stroke severity of patients receiving thrombolysis at Bispebjerg Hospital.

Statistics

The propensity score is the conditional probability of assignment to a particular treatment given a vector of observed covariates. Both large and small sample theory shows that adjustment for the scalar propensity scores is sufficient to remove bias due to all observed covariates. For the superiority analysis, the sample size is driven by the availability of patients. We estimate of having between 100 and 150 propensity score matched pairs. Propensity scores for undergoing thrombectomy or IV thrombolysis only are estimated with a probit model. We use Cox proportional hazards models to derive hazard ratios comparing the two groups, crude and adjusted, with the inverse probability of treatment (IPT) as weight in the analysis of all patients and accounting for the 1:1 matching in the analysis of propensity score-matched patients.

Sample size

We estimate that between 100 and 150 matched pairs are sufficient for the analyses. This figure is based on an assumed 30% absolute difference in favorable three-months outcomes between the two treatment groups. We anticipate the sufficient number of patients treated with IV-tPA in the period will be available in the database at Bispebjerg Hospital. In the event of need for additional endovascular patients, those treated at Lund, Sweden, will be included in the analysis.

Registration

No registration required.

Ethics

No ethical concerns due to the strictly retrospective character of the analysis.

Duration

Between two and three years.

Mentors

[redacted]

Regional Collaborators

[redacted]

[redacted]

International Collaborators

[redacted]

Additional secondary projects

Effectiveness of intravenous thrombolysis for patients with acute ischemic stroke and occlusion on CTA

A comparative analysis of pre-thrombolytic CTA and pre-procedural DSA.

Description

According to current guidelines, patients demonstrating acute neurological signs and symptoms of stroke should be considered for intravenous (IV) thrombolysis, and are required to undergo a non enhanced cerebral computer tomography (CT), to exclude intracranial hemorrhage and other differential diagnosis (6-8). In the acute phase of an ischemic stroke, radiological CT-signs are usually absent, except in some cases when a severe occlusion in the anterior circulation gives rise to 'early infarct signs', or when a thrombus in the anterior or posterior circulation can be seen as a "dense artery sign" (9-17). In the Copenhagen area, such patients are transferred to a thrombolysis center, if not already re-routed there, and IV thrombolysis is initiated if no contraindications exist. The stroke severity is assessed using the National Institute of Health Stroke Scale (NIHSS) and further therapeutic decisions depend on the results of the NIHSS score. Since endovascular thrombectomy became available in June 2011, a CT angiogram (CTA) is performed along with the initial diagnostic CT or prior to the decision to refer a patient to receive intra-arterial (IA) thrombolysis ('bridging') and/or thrombectomy at the endovascular treatment center at Rigshospitalet. A referral is usually considered if the patient presents with a large vessel target occlusion and severe neurological symptoms, i.e. NIHSS > 9 (at least moderate stroke severity) not responding to IV thrombolysis. Typically, the effect of IV thrombolysis is assessed 30 minutes after a bolus or infusion of Actilyse. Following transferral to the endovascular treatment center, the neurological status is reassessed and in case the neurological status has not improved, a digital subtraction angiography (DSA) is performed in preparation of the IA thrombolysis/thrombectomy. A 90-day post-treatment clinical followup is performed, including a modified Rankin Score (mRS) (6-8). The current treatment protocol at our institution is evolving according to international guidelines and allows to assess the efficacy of intravenous tissue plasminogen activator (IV-tPA) to resolve large vessel

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occlusions in all patients considered for IA thrombolysis/thrombectomy after ineffective IV thrombolysis (18, 19).

Despite the thorough clinical and radiological evaluation of the patient before and after 'bridging' therapy and/or thrombectomy, it has so far not been possible to predict the likely outcome of the treatment based on the pre-treatment DSA. Thus it remains uncertain whether the chances of a beneficial outcome will exceed the risk of adverse effects. Further, the experience of many stroke specialists that the outcome of thrombolysis and thrombectomy depends on the degree of leptomeningeal collateralization, which yet remains to be quantitatively investigated.

The comparison of findings on the CTA, pre- and post-DSA allows a quantitative correlation between vascular radiological findings, clinical findings and the determination of efficacy of IV thrombolysis and thrombectomy. The collateral vasculature is estimated by applying the effective and unbiased volumetric stereological methods on the CTA images. By these means we will be able to predict the likely outcome of the treatment, and allocate patients to thrombolysis and/or thrombectomy who are likely to experience a beneficial outcome of the treatment, thus avoiding severe adverse events.

Aims

- To quantify the thrombus and the collateral vasculature on the CTA and the pre- and post treatment DSA in patients with acute ischemic stroke by means of stereological techniques.
- To describe the effect of IV thrombolysis on vascular reperfusion in patients who do not clinically respond to the treatment.
- To describe the effect of 'bridging' IV thrombolysis and IA thrombectomy on vascular reperfusion in patients with limited pre-treatment collateral blood flow.
- To describe the effect of 'bridging' thrombolysis and thrombectomy on short term NIHSS and long term mRS in patients with limited pre-treatment collateral blood flow.
- To describe the effect of 'bridging' thrombolysis and thrombectomy on short term NIHSS and long term mRS in patients with lack of reperfusion.

Methods

The study is a retrospective, observational cohort study conducted from January 2009 to January 2013 at three Copenhagen area hospitals as part of the Copenhagen acute severe stroke intervention study (CPH-ASSIST). The cohort investigated and the data on the patients is obtained from the same sources as in the CPH-ASSIST main study, and the data analysis is performed according to this. The aim of the study is to identify the location and measure the dimensions of the thrombus in patients with acute ischemic stroke. Further, we identify the presence and quantify the degree of collateral vasculature on the pre-treatment CTA and compare it to the pre- and post-treatment DSA. Patients who met clinical and radiographic criteria but did not undergo a post-treatment DSA are registered to determine the ratio of initially successful clinical responses with IV-tPA alone. The dimensions of the thrombus and the collateral vasculature are quantified by applying unbiased stereological volumetric technics on the CT angiogram. By superimposing a counting grid upon the CTA images, the total length, number and volume of the collateral vasculature are estimated using Cavalieri's principle (20) and the findings are correlated to the pre- and post treatment DSA and clinical response.

Safety of multimodality endovascular intervention following intravenous thrombolysis in acute stroke patients

A comparative multivariate analysis of patients undergoing 'bridging' thrombolysis and subsequent interventions in terms of outcome and complications.

Description

The beneficial effect of thrombolysis and thrombectomy in the treatment of acute ischemic stroke is potentially of major significance on morbidity and mortality (21). However, the same is true regarding the adverse effects (22). A number of adverse effects from intravenous (IV) thrombolysis have been reported, of which the most severe in terms of morbidity and mortality are angio-oedema, symptomatic intracerebral hemorrhage (sICH) and fatal symptomatic intracerebral hemorrhage (23). Due to the systemic appliance of IV thrombolysis, severe extra-cerebral adverse effects are likely to be encountered as well, such as gastrointestinal-, urinary tract -, and retroperitoneal hemorrhage (24). Added to this are the potentially severe adverse effects of subsequent endovascular treatment. Local complications caused by catheter- and guidewire insertion and manipulation may result in hematoma, infection, perforation and dissection of the artery wall, as well as dislodging of atherosclerotic plaques and secondary cerebral embolism. In the cerebral circulation, thrombectomy and angioplasty may cause vasospasm, embolization, perforation, stent thrombosis, dissection and pseudoaneurysm (24). The patient is at risk of cardiac- and pulmonary complications related to general anesthesia, and the contrast media and medication may cause allergic reaction. Initially successful recanalization can later exacerbate tissue injury by promoting reperfusion injury, excessive cerebral edema and hemorrhagic transformation (25). Our current knowledge of the disability and expenses of the adverse effect are considerable, and a relatively small margin exist between the number needed to treat and the number needed to harm. Major trials, including the studies upon which the current international guidelines are based, mention the 90-day outcome for patients treated with thrombolysis ranging from 2.4% - 24.9% regarding sICH, 7.7% - 22.3% regarding mortality and 34% - 54.8% regarding independence (26). However, the methodology of several of the studies have been exposed to criticism and the beneficial outcomes reported have been doubted (19). Even though endovascular treatment in terms of thrombectomy in conjugation with 'bridging' thrombolysis in patients with complete occlusion of a large cerebral artery have show to be overall more efficient than treatment with thrombolysis only, the adverse events are added as well. The current studies do not succeed in comparing the overall beneficial and adverse effects in terms of mortality and morbidity in a rigorous and strong study design. Further, it remains uncertain whether a subgroup of patients would be more likely to benefit from the treatment or more likely to experience an overall harmful effect. The main aim of the study is to be able to stratify patients at special risk and thereby avoid subjecting them to a treatment of which the risk of severe disability and death exceeds the potential benefits.

Aims

- To determine the incidence of severe systemic and local adverse effects within 30 days following thrombectomy and angioplasty after 'bridging' therapy, with emphasis on symptomatic- and fatal hemorrhage and death.
- To identify patients at especially high risk of severe adverse events based on patients' characteristics.
- To determine the influence of the duration of the endovascular procedure on severe adverse effects and death within 30 days following the procedure.

Methods

The study is a retrospective, observational cohort study conducted from January 2009 to January 2013 at three Copenhagen area hospitals as part of the Copenhagen acute severe stroke intervention study (CPH-ASSIST). The cohort investigated and the data on the patients is obtained from the same sources as in the CPH-ASSIST main study, and the data analysis is performed according to this. We will perform a comparative analysis of the occurrence of complications and adverse effects in various forms of endovascular interventions performed after IV thrombolysis.

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Time delays in endovascular treatment of patients with acute ischemic stroke

An analysis of time delays associated with patient transfer and treatment in the **C**o**p**en**h**agen **a**cute **s**evere **s**troke **i**ntervention **st**udy (CPH-ASSIST).

Description

It is a well established fact that time is the most significant factor in determining the clinical outcome in patients suffering from acute ischemic stroke (27-32). According to most guidelines, intravenous (IV) thrombolysis must be initiated within four and a half hour from the onset of symptoms (6, 21, 33). In order to reduce the pre-hospital delays, the hospitals and medical emergency services (EMS) in the Copenhagen area have procedures ensuring the fastest possible diagnosis, initiation of thrombolysis and referral to the neuroradiology department at the Copenhagen University Hospital, Rigshospitalet, for thrombectomy (7, 8). The infrastructure and means of transportation in the Copenhagen area is well-developed and ensures, at least in theory, relatively short average pre-hospital delays. However, these are not the only obstacles in the process of receiving the proper treatment. Previous studies have shown that on arrival the patient may experience several significant in-hospital delays, e. g. delays in medical assessment, neuroimaging, and transfer of the patient to the catheterization laboratory (34-41). Although these in-hospital barriers are likely to be of importance at the referring hospitals, they are not encountered to a great extent when referred to the interventional facility at Rigshospitalet, since the patient is transferred directly to the room for intervention and the endovascular treatment.

Streamlining the diagnostic approach and transfer of the patient is critical to keep delays from needle to groin stick at bay. In order to understand the difficulties in the implementation of a more efficient stroke management, a critical analysis of time delays is essential. In addition, learning about the circadian characteristics and variations between weekday versus weekend/holiday occurrence of severe stroke are important to allocate necessary resources.

However, so far no study has investigated the specific pre-hospital and in-hospital delays and the impact of the delays on the patient outcome in the Copenhagen area. Hence is remains unknown wether and to which extent there is potential for a reduction of the delay to treatment, both at the larger scale and between the referring hospitals and interventional center. Further, it remains unclear whether 'bridging' therapy extends the time window, due to the lack of randomized trials on the subject. However, reducing time to initiation of IV thrombolysis improves the outcome of 'bridging' therapy, as demonstrated in a recent meta-analysis (5). It is therefore safe to conclude that delays in the management of patients prior to 'bridging' therapy should be kept at a minimum. In this study we gather information on several pre- and in-hospital delays. The current average delays are compared to the ideal situation in which the only delay is from arrival at the interventional room to the initiation of the digital subtraction angiography (DSA). With this study we provide the evidence based foundation for a reduction of the current time to treatment and the future infrastructural health care planning.

Aims

- To describe the circadian rhythms in the management of stroke patients referred to thrombectomy after 'bridging' therapy compared to patients receiving IV-tPA only.
- To describe the influence of on-versus off-hours and weekend/holiday versus weekday hours of admission of stroke patients referred for thrombectomy after 'bridging' therapy compared to patients receiving IV-tPA only.
- To describe the pre-hospital and in-hospital delays in the management of stroke patients referred to thrombectomy after 'bridging' therapy.
- To estimate of the lack of improvement per time unit compared to an ideal situation with no delays.

Methods

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The study is a retrospective, observational cohort study conducted from January 2009 to January 2013 at three Copenhagen area hospitals as part of the Copenhagen acute severe stroke intervention study (CPH-ASSIST). The cohort investigated and the data on the patients is obtained from the same sources as in the CPH-ASSIST main study, and the data analysis is performed according to this. The time of EMS arrival at the scene was recorded on the EMS records and in the hospital records. Time of ED admission was recorded as the time the patient was registered at the ED, and the time of first ED physician consultation was registered in the hospital record. It was registered weather the primary physician consultation was at a thrombolysis center or at a non-thrombolytic center (e. g. a medical or neurological department) and time of first neurological consultation at the thrombolytic center was registered. The time from ED admission to the acquisition of the emergency CT was obtained from the CT log and the time from completion of the emergency CT to arrival at the interventional department was obtained from the hospital records and papers from the EMS. Finally, the time intervals from arrival at the interventional room to the pre-treatment DSA and the time from the pre- to post-treatment DSA was recorded from the hospital records.

References

1. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA : the journal of the American Medical Association. 2003;290(24):3207-14. Epub 2003/12/25.
2. Wahl A, Juni P, Mono ML, Kalesan B, Praz F, Geister L, et al. Long-term propensity score-matched comparison of percutaneous closure of patent foramen ovale with medical treatment after paradoxical embolism. Circulation. 2012;125(6):803-12. Epub 2012/01/13.
3. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. The New England journal of medicine. 2012;366(11):991-9. Epub 2012/03/16.
4. Lyden P. Editorial on "A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes". Stroke; a journal of cerebral circulation. 2012;43(3):621-2. Epub 2012/02/22.
5. Mazighi M, Meseguer E, Labreuche J, Amarenco P. Bridging therapy in acute ischemic stroke: a systematic review and meta-analysis. Stroke; a journal of cerebral circulation. 2012;43(5):1302-8. Epub 2012/04/25.
6. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovascular diseases (Basel, Switzerland). 2008;25(5): 457-507. Epub 2008/05/15.
7. Stroke DSf. Danish Reference Program for Treatment of Stroke. 2009.
8. Board DH. National Danish Guidelines for Treatment With Thrombolytic Agents in Acute Ischemic Stroke. 2008.
9. Bakshi R, Mazziotta JC. Acute middle cerebral artery thrombosis demonstrated by cranial computed tomography: the "dense MCA" sign. Archives of neurology. 1998;55(12):1577. Epub 1998/12/29.
10. Bettle N, Lyden PD. Thrombosis of the posterior cerebral artery (PCA) visualized on computed tomography: the dense PCA sign. Archives of neurology. 2004;61(12):1960-1. Epub 2004/12/15.
11. Bodensteiner JB, Reitter BF, Sheth RD. Basilar artery occlusion and the dense artery sign in the newborn. Clinical pediatrics. 1998;37(9):551-4. Epub 1998/10/17.
12. Koo CK, Teasdale E, Muir KW. What constitutes a true hyperdense middle cerebral artery sign? Cerebrovascular diseases (Basel, Switzerland). 2000;10(6):419-23. Epub 2000/11/09.
13. Launes J, Ketonen L. Dense middle cerebral artery sign: an indicator of poor outcome in middle cerebral artery area infarction. Journal of neurology, neurosurgery, and psychiatry. 1987;50(11):1550-2. Epub 1987/11/01.
14. Zorzon M, Mase G, Pozzi-Mucelli F, Biasutti E, Antonutti L, Iona L, et al. Increased density in the middle cerebral artery by nonenhanced computed

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tomography. Prognostic value in acute cerebral infarction. European neurology. 1993;33(3):256-9. Epub 1993/01/01.

15. Schuknecht B, Ratzka M, Hofmann E. The "dense artery sign"--major cerebral artery thromboembolism demonstrated by computed tomography. Neuroradiology. 1990;32(2):98-103. Epub 1990/01/01.
16. Moonis M, Fisher M. Imaging of acute stroke. Cerebrovascular diseases (Basel, Switzerland). 2001;11(3):143-50. Epub 2001/04/18.
17. Moulin T, Cattin F, Crepin-Leblond T, Tatu L, Chavot D, Piotin M, et al. Early CT signs in acute middle cerebral artery infarction: predictive value for subsequent infarct locations and outcome. Neurology. 1996;47(2):366-75. Epub 1996/08/01.
18. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane database of systematic reviews (Online). 2009(4):CD000213. Epub 2009/10/13.
19. Fatovich DM. Believing is seeing: Stroke thrombolysis remains unproven after the third international stroke trial (IST-3). Emergency medicine Australasia : EMA. 2012;24(5):477-9. Epub 2012/10/09.
20. Gundersen HJ, Jensen EB. The efficiency of systematic sampling in stereology and its prediction. Journal of microscopy. 1987;147(Pt 3): 229-63. Epub 1987/09/01.
21. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. The New England journal of medicine. 2008;359(13):1317-29. Epub 2008/09/26.
22. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369(9558):275-82. Epub 2007/01/30.
23. Bray BD, Campbell J, Hoffman A, Tyrrell PJ, Wolfe CD, Rudd AG. Stroke thrombolysis in England: an age stratified analysis of practice and outcome. Age and ageing. 2012. Epub 2012/11/24.
24. Darkhabani Z, Nguyen T, Lazzaro MA, Zaidat OO, Lynch JR, Fitzsimmons BF, et al. Complications of endovascular therapy for acute ischemic stroke and proposed management approach. Neurology. 2012;79(13 Suppl 1):S192-8. Epub 2012/10/04.
25. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke; a journal of cerebral circulation. 2007;38(3): 967-73. Epub 2007/02/03.
26. Micieli G, Marcheselli S, Tosi PA. Safety and efficacy of alteplase in the treatment of acute ischemic stroke. Vascular health and risk management. 2009;5(1):397-409. Epub 2009/05/30.
27. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. Stroke; a journal of cerebral circulation. 1981;12(6):723-5. Epub 1981/11/01.
28. Jones TH, Morawetz RB, Crowell RM, Marcoux FW, FitzGibbon SJ, DeGirolami U, et al. Thresholds of focal cerebral ischemia in awake monkeys. Journal of neurosurgery. 1981;54(6):773-82. Epub 1981/06/01.
29. Mazighi M, Serfaty JM, Labreuche J, Laissy JP, Meseguer E, Lavallee PC, et al. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. Lancet neurology. 2009;8(9):802-9. Epub 2009/08/04.
30. The Interventional Management of Stroke (IMS) II Study. Stroke; a journal of cerebral circulation. 2007;38(7):2127-35. Epub 2007/05/26.
31. Costalat V, Lobotesis K, Machi P, Mourand I, Maldonado I, Heroum C, et al. Prognostic factors related to clinical outcome following thrombectomy in ischemic stroke (RECOST Study). 50 patients prospective study. European journal of radiology. 2012. Epub 2012/09/04.
32. Emergency brain resuscitation. A Working Group on Emergency Brain Resuscitation. Annals of internal medicine. 1995;122(8):622-7. Epub 1995/04/15.
33. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation. 2007;115(20):e478-534. Epub 2007/05/23.
34. Wester P, Radberg J, Lundgren B, Peltonen M. Factors associated with delayed admission to hospital and in-hospital delays in acute stroke and TIA: a prospective, multicenter study.Seek- Medical-Attention-in-Time Study Group. Stroke; a journal of cerebral circulation. 1999;30(1):40-8. Epub 1999/01/08.
35. Evenson KR, Foraker RE, Morris DL, Rosamond WD. A comprehensive review of prehospital and in-hospital delay times in acute stroke care. International journal of stroke : official journal of the International Stroke Society. 2009;4(3):187-99. Epub 2009/08/08.
36. Evenson KR, Rosamond WD, Morris DL. Prehospital and in-hospital delays in acute stroke care. Neuroepidemiology. 2001;20(2):65-76. Epub 2001/05/19.
37. Jungehulsing GJ, Rossnagel K, Nolte CH, Muller-Nordhorn J, Roll S, Klein M, et al. Emergency department delays in acute stroke - analysis of time between ED arrival and imaging. European journal of neurology : the official

journal of the European Federation of Neurological Societies. 2006;13(3): 225-32. Epub 2006/04/19.

38. Nolte CH, Malzahn U, Kuhnle Y, Ploner CJ, Muller-Nordhorn J, Mockel M. Improvement of Door-to-Imaging Time in Acute Stroke Patients by Implementation of an All-Points Alarm. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2011. Epub 2011/09/10.
39. Romano JG, Muller N, Merino JG, Forteza AM, Koch S, Rabinstein AA. In-hospital delays to stroke thrombolysis: paradoxical effect of early arrival. Neurological research. 2007;29(7):664-6. Epub 2008/01/05.
40. Ratanakorn D, Keandoungchun J, Sittichanbuncha Y, Laothamatas J, Tegeler CH. Stroke fast track reduces time delay to neuroimaging and increases use of thrombolysis in an academic medical center in Thailand. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2012;22(1):53-7. Epub 2010/12/03.
41. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. Age and ageing. 2004;33(2):116-21. Epub 2004/02/13.